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Original Research

Real-world efficacy and safety of lenvatinib: data from a compassionate use in the treatment of radioactive iodine-refractory differentiated thyroid cancer patients in Italy

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KEYWORDS
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Abstract ***Background:*** Lenvatinib is a multi-kinase inhibitor approved for patients with radioactive iodine (RAI)–resistant differentiated thyroid cancer (DTC). Before the drug approval from the Italian National Regulatory Agency, a compassionate use programme has been run in Italy. This retrospective study aimed to analyse data from the first series of patients treated with lenvatinib in Italy.
Methods: The primary aim was to assess the response rate (RR) and progression-free survival (PFS). Secondary end-points include overall survival (OS) and toxicity data.
Results: From November 2014 to September 2016, 94 patients were treated in 16 Italian sites. Seventeen percent of patients had one or more comorbidities, hypertension being the most common (60%). Ninety-eight percent of patients were treated by surgery, followed by RAI in 98% of cases. Sixty-four percent of patients received a previous systemic treatment. Lenvatinib was started at 24 mg in 64 subjects. Partial response and stable disease were observed in 36% and in 41% of subjects, respectively; progression was recorded in 14% of patients. Drug-related side-effects were common; the most common were fatigue (13.6%) and hypertension (11.6%). Overall, median PFS and OS were 10.8 months (95% confidence interval [CI], 7.7–12.6) and 23.8 months (95% CI, 19.7–25.0) respectively.
Conclusion: Lenvatinib is active and safe in unselected, RAI-refractory, progressive DTC patients in real-life setting. RR and PFS seem to be less favourable than those observed in the SELECT trial, likely due to a negative selection that included heavily pretreated patients or with poor performance status.

1. Introduction

Differentiated thyroid cancer (DTC) is a rare human malignancy, but it is the most common malignant tumour within the thyroid neoplasms. In the last years, its incidence significantly increased worldwide [1], even in Italy [2], mainly due to an overdiagnosis of papillary microcarcinoma. In Europe, the 5-yr relative survival (RS) ranges from 98% to 92% in women and from 94% to 88% in men, according to the histological variant, papillary versus follicular [2]. In Italy, almost 15.300 new cases of thyroid cancer were expected in 2017; the 5-years RS was 90% for men and 95% for women [3]. About 20% of DTC patients have a locoregional recurrence and/or distant metastases [4,5]. Prognosis remains favourable when lesions are radioactive iodine (RAI)-avid, but unfortunately two-thirds of them become RAI-refractory, and in those patients, the 10-year survival rate drops to <10% [4], with a mean life expectancy of 3–5 years [6].

Surgery, external beam radiation and locoregional treatments are indicated for well-localised disease, with limited-tumour burden, while systemic therapies are currently effective to control metastatic, progressive, symptomatic and/or imminently life-threatening disease [7].

Lenvatinib is an investigational, oral multitargeted kinase inhibitor (MKI) of vascular endothelial growth factor receptor 1–3, fibroblast growth factor-R 1–4, platelet-derived growth factor-Rα, REarraged during Transfection (RET) and c-Kit that interferes with angiogenesis and lymphangiogenesis and controls cell proliferation [8,9]. It has been approved for the treatment of locally recurrent or metastatic, progressive RAI resistance-DTC in the United States, Europe and Japan, based on the meaningful results from the randomised SELECT trial [10]. In this study, lenvatinib (24 mg/die, for 28-day cycles) significantly improved the progression-free survival (PFS) compared to placebo (18.3 versus 3.6 months, hazard ratio [HR] 0.21, 99% confidence interval [CI] 0.14–0.31, $p < 0.001$), reducing the probability of disease progression of 79%. The response rate (RR) was 64.8% in the treatment arm versus 1.5% in the placebo arm ($p < 0.001$), significantly reducing the tumour burden, with a median maximum percentage change in tumour size of −42.9% [10]. The efficacy of lenvatinib was recently confirmed even in specific patients' population, such as elderly (>65 years old) with a significant increase in overall survival (OS), compared to placebo ($p = 0.020$), demonstrating for the first time a survival improvement with an MKI in RAI-resistant DTC patients.

It has been widely acknowledged that results derived from controlled clinical trials are rarely repeatable in the real life because these trials are usually conducted in selected populations, in a highly controlled setting, optimised to show the effect of the drug [11]. However, real-world evidence has increased its relevance during the years. The European Medicines Agency considers the real-world data as a crucial element in the monitoring of drugs. Indeed, real-world data may contribute to increase the external validity of randomised trials and could be potentially useful in the pathway of drug approval and cost reimbursement [12].

To this end, we retrospectively reviewed all relevant clinical outcomes of patients who participated in the lenvatinib compassionate use programme prior to the commercialisation of the drug in Italy.

2. Materials and methods

2.1. Patients

This retrospective study included data from patients who participated in the compassionate use programme in 16 Italian sites. Only sites in which at least three patients were managed have been considered for this observational study. Inclusion/exclusion criteria were equal to those of the SELECT trial except the enrolment of patients previously treated with one or more systemic therapy. Inclusion criteria were patients older than 18 years and histologically or cytologically confirmed diagnosis of DTC. RAI-refractory disease; progressive disease within the last 12 months; Eastern Cooperative Oncology Group (ECOG) PS 0–2, blood pressure $\leq$150/90 mm Hg and creatinine clearance $\geq$30 mL/min (Cockcroft and Gault formula) and adequate bone marrow and liver function were even required. One prior line of systemic therapy was allowed. Exclusion criteria were proteinuria (urine protein $\geq$ 1 g/24 h), history of congestive heart failure, unstable angina, myocardial infarction, serious cardiac arrhythmia or stroke within the past 6 months; QT interval prolongation in the electrocardiogram; existing anticancer therapy-related toxicities of grade $\geq$ II and history of intolerance to or progression on prior treatment with lenvatinib. Common toxicity criteria, v4.03, were applied to grade the side-effects. All patients signed a written informed consent and the study was approved by local ethics committees.

2.2. Treatment

Recommended dose for lenvatinib was 24 mg/day; dose reduction occurred in succession, based on the previous dosage (20, 14 and 10 mg/day) and in presence of intolerable toxicity. Lenvatinib continued as long as it was clinically appropriate, based on tumour assessment (until disease progression or inadequate therapeutic effect and in presence of unacceptable side-effects) and judgement of the treating physician.

2.3. Statistical analysis

The primary aim was to compare data from real life and the SELECT study in terms of RR and PFS. Secondary end-points include OS and toxicity data. Descriptive statistics were used for continuous variables, using mean, standard deviation, median, interquartile range and minimum and maximum values. Categorical variables were summarised as number and percentage and 95% confidence limits for continuous data and proportions were presented where appropriate.

3. Results

3.1. Patients characteristics and response to therapy

From November 2014 to September 2016, 94 patients were enrolled in the compassionate use at 16 Italian sites. Demographic and clinical baseline characteristics are summarised in Table 1. The total period of patient data collection was 36 months, and this time frame concerns to the 'day of the first patient treated' until the 'day of the last patient collection data'. Median age at the enrolment was 60 years (range 22–82), with 26 patients older than 65 years (27.6%); forty-six patients were women (49%). Hypertension was reported in 60% of patients, and 10 patients had a previous tumour and among those, 6 had breast cancer. All patients had metastatic disease with a disease progression within the last 12 months. Ninety-eight percent of patients underwent surgery, and 98% received RAI. Two patients did not receive RAI due to unresectable disease. 64% of patients received previous systemic therapies, where kinase inhibitors were the most administered, with sorafenib prescribed in 61% of the cases. A response to lenvatinib was observed since the first evaluation that was performed in a variable range of 2–4 months, based on the site's policy on treatment assessment. Best response was partial in 34 patients (36%), stable disease in 39 patients (41%) and progression disease in 13 patients (14%); response was not evaluable in 8 patients (Table 2). No complete remission was observed. Median OS was 23.8 months (95% CI 19.7–25.0 -); 6-month and

Table 1
Demographic and clinical baseline characteristics.

Patients	N. 94
Female	46
Median age, years (range)	60 (23–82)
ECOG PS 0–1	85%
ECOG PS 2	15%
Body mass index, mean	26.3
Primary treatment:	
Surgery	98%
Radioactive iodine	98%
Systemic therapy	64%
Sorafenib	61%
Chemotherapy	22%
Vandetanib	18.3%
Sunitinib	8.3%
Other	13.3%
Comorbidities:	
Hypertension	60%
Diabetes	14%
Diverticula (abdominal or oesophageal)	2%
Gallbladder stones	2%
Previous tumour	13.7%

ECOG, Eastern Cooperative Oncology Group.

Table 2
Efficacy of lenvatinib in EAP Italy compared to the SELECT trial [10].

	EAP Italy (n = 94)	SELECT (n = 169)
Complete response, n (%)	0	4 (1.5)
Partial response, n (%)	34 (36)	165 (63.2)
Stable disease, n (%)	39 (41)	60 (23.0)
Progression disease, n (%)	13 (14)	18 (6.9)
Not evaluable (ne), n (%)	8 (9)	14 (5.4)
PFS months (95% CI)	10.8 (7.7–12.6)	18.3 (15.1-ne)
OS months (95% CI)	23.8 (19.7–25.0)	ne (22.0-ne)
6-month survival (%)	93.5	90.7
12-month survival (%)	91.7	81.6

PFS, progression-free survival; OS, overall survival; CI, confidence interval; EAP, expanded access program.

12-month survival was 94% and 92%, respectively. Median PFS was 10.8 months (95% CI 7.7–12.6) (Fig. 1).

Patients with clinical characteristics suitable for the enrolment in the SELECT trial were 54 (57.44%), 21 naive and 33 pretreated. In this subgroup, partial response was 35%, stable disease, 37% and disease progression, 11.1% (3 cases were lost to follow-up). The median PFS was 11.9 months (95% CI 8.2–12.9 months), and the median OS was 24.2 months (95% CI 20–25.5 months). The activity of lenvatinib was confirmed, regardless if patients were previously treated or not ($p > 0.05$). One-year survival in younger (≤65 years) and older (>65 years) patients was 92% and 89%, respectively, with a median survival of 22.2 months (95% CI 18.3–25 months) versus 24.8 months (95% CI 18.3–29.2 months), respectively. Five was the median number of enrolled patients. Interestingly, the median OS in patients treated in those sites, where at least 5 patients were enrolled, was 24.1 months (95% CI 18.3–25.5), while the median OS of patients managed in sites with <5 patients was 22.6 months (95% CI 19.4–26.2) ($p > 0.05$)

At the cut-off date (December 2017), 54.2% patients were alive and 36 of these patients (49.3%) continued with commercial product; 44.3% died, while 3.4% patients were lost to follow-up.

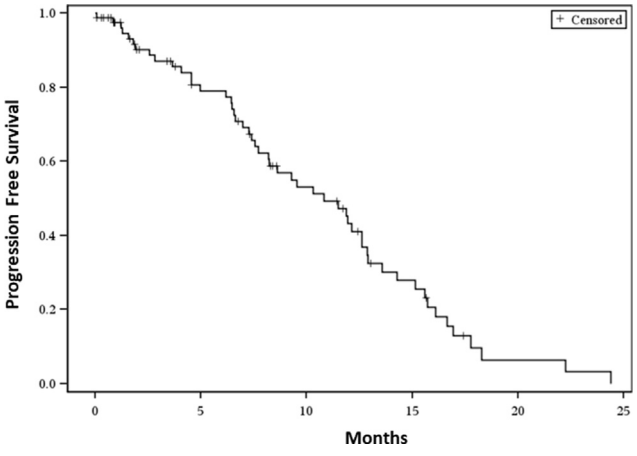

Fig. 1. Kaplan-Meier curve of progression free survival.

3.2. Compliance to lenvatinib

Compliance to lenvatinib was assessed on 90 patients. The initial dose of lenvatinib was 24 mg for 64 patients (71.1%), 20 mg for 10 patients (11.1%) and 14 mg for 11 patients (12.2%); five patients started at 10 mg or less. Reasons conditioning a starting dose lower than 24 mg were diverse: 7 patients were older than 70 years; 7 patients had serious cardiovascular comorbidities (including 1 patient with a suspicious pulmonary thromboembolism); 3 patients were heavily pretreated; one patient had even 4000 platelets due to bone marrow involvement; 2 patients had an increased risk of tumour-related bleeding; surgery and local laser have been done in 2 patients with tracheal disease; impairment of renal function was present in one patient and shortage of 4-mg pills was the reason in 3 other cases.

The median daily dose was 19.2 mg (range 10–24 mg). Dosing was reduced in 62 patients, with a median reduction of 41.7% from baseline, while it was increased in 4 patients. Seven patients did not change dosage. The median duration of treatment was 176 days (range 2–913 days).

3.3. Toxicity

Eighty-two patients of 94 were evaluable for toxicity and presented at least one adverse event (AE). A total of 461 AEs of any grade were accounted; at least one AE of grade ≥III was observed in 21 patients (22.3%). Serious adverse events (SAEs) were reported in 26 patients; among SAEs, 5 were considered as drug related: tracheal bleeding, pulmonary embolism, tracheoesophageal fistula, wound healing impairment and cardiac flutter. The most frequent AEs (both AE and SAE) were fatigue (13.4%) and hypertension (11.7%) (Table 3). No grade V toxicity has been reported.

4. Discussion

Lenvatinib was approved by the US Food and Drug Administration in August 2015 for RAI-resistant-

Table 3
Adverse events (N° = 461).

AE description All grade	EAP Italy N (%)[a]	EAP Italy Grade ≥ G3 (%)[a]	SELECT Study Grade ≥ G3%
Fatigue	62 (13.4)	34 (8.2)	9.2
Hypertension	54 (11.7)	22 (4.7)	41.8
Diarrhoea	33 (7.1)	13 (2.8)	8.0
Stomatitis	32 (6.9)	20 (4.3)	4.2
Decreased weight	32 (6.9)	21 (4.5)	9.6
Hand-foot syndrome	26 (5.6)	9 (1.9)	3.4
Decreased appetite	24 (5.2)	14 (3.0)	5.4
Nausea	19 (3.4)	6 (1.3)	2.3
Proteinuria	15 (3.2)	8 (1.7)	10.0

[a] Percentages were calculated according to the total number of side-effect events.

progressive DTC patients due to the impressive results obtained in the randomised trial SELECT with a significant PFS advantage for those patients treated with the drug compared to placebo (HR 0.21 99% CI 0.14–0.31). This retrospective observational study confirms the efficacy of lenvatinib in RAI-refractory, progressive, unselected DTC patients in a real-world practice in Italy. Global results, however, are inferior to those reported in the SELECT trial [10], being ORR 36% versus 64% and median PFS 10.8 months versus 18 months.

Indeed, our real-life population was more compromised for clinical characteristics from patients enrolled in the SELECT trial, in particular 15% of patients had ECOG PS 2 in comparison to 5%; 64% of patients have already received at least one systemic treatment versus 25.3%. Moreover, only 71.1% of the patients started lenvatinib at 24 mg.

Interestingly, general patients' characteristics and clinical outcomes were consistent to those reported in a real-life experience carried out in France [13]. In this latter study, among 75 evaluable subjects, 16% had an ECOG PS $\geq$ 2 and 68% received at least one prior line of therapy; the response rate was 31%, and the median PFS was 10 months. In both Italian and French experiences, lenvatinib was started late in heavy pretreated patients, with more advanced disease and worst general conditions. Indeed, the median PFS in Italian and French series is similar to the median PFS of 10.8 months of patients receiving lenvatinib after the crossover [10]. Analogous results were reported in a smaller series of 13 patients collected in Switzerland where RR was 31% and median PFS 7.2 months [14]. The advanced disease, prior treatments, and worst general conditions may unavoidably impact on drug compliance (e.g. lower starting dosages, more drug interruptions) and, therefore, on treatment effect.

Alike in the SELECT trial, we have been able to confirm the activity of lenvatinib in all patients, regardless of previous systemic treatments and age. Indeed, this latter ($\leq$65 and >65 years) was a stratification factor in the SELECT trial and lenvatinib was the first agent to demonstrate an advantage in survival in patients with RAI-resistant DTC older than 65 years; in particular, OS was improved compared to the placebo arm (HR, 0.53; 95% CI, 0.31 to 0.91; p = 0.020 [15]. No differences in survival were observed when we compared younger ($\leq$65 years) versus older patients (>65 years) in our population, supporting the activity of lenvatinib even in a real-life population of older patients.

Side-effects involved at least all evaluable patients. The rate of AEs of grade $\geq$III are globally lower compared to that reported in SELECT trial (Table 3).This could be a secondary effect of the initial underdosing of lenvatinib or an intrinsic limit of a retrospective data collection. Fatigue followed by hypertension was the most commonly reported AEs, and only 15 episodes of proteinuria were accounted during the study. Noteworthily, fatigue was the most common drug-related AE both in our series and in French one, differently from the SELECT trial where hypertension was first [10]. From experiences in the SELECT trial and clinicians have learnt to prevent or manage hypertension with antihypertensive agents; fatigue, however, continues to be one of the most distressing AEs to control and, indeed, a similar rate for $\geq$ G3 events has been reported both in SELECT and in real-life practice.– Common during antiangiogenic agents, fatigue cannot be managed with effective treatments, except for psychoeducational approaches. Thyroid function imbalance, as well as other endocrine side-effects—i.e. adrenal function impairment—may contribute to fatigue in this specific population. Some authors would exclude lenvatinib from treatment for patients with a higher risk of tracheoesophageal fistula or bowel rupture, especially in presence of diverticula [16]. Although few cases (2%) of patients had a diagnosis of diverticula at baseline, we did not observe any specific side-effects as fistula or gastrointestinal perforation. The presence of diverticula should be investigated by CT scan during the staging procedure, but in the lack of active inflammation symptoms, diverticula seem to not represent a relative contraindication to lenvatinib.

Antiangiogenic compounds have a relevant side-effect profile, and physician's experience is required to guarantee the optimal patient compliance, avoiding treatment interruptions and/or dose reductions.

RAI-resistant DTC is considered a rare malignant tumour according to the RARECARE definition (incidence rate < 6/100.000 year) [17], and, as such, it should be managed only in referral sites. It was already known for different rare tumours such as head and neck cancers, for example, how the experience of the treating sites could make the difference for the patients' outcome [18]. We observed a trend to a better OS, although not statistical significant, in patients treated in sites with 5 or more enrolled subjects. This observation, if will be confirmed, suggests that similarly to other rare tumours, also RAI-resistant, progressive, DTC patients may benefit to be managed in high-volume referral sites within a multidisciplinary team.

5. Conclusions

Lenvatinib is active even in a real-life RAI-refractory, progressive, metastatic unselected DTC population, including subjects older than 65 years and pretreated patients; toxicities were common but manageable. The activity of lenvatinib could be improved if the drug administration started in the early phase of RAI-refractory disease.

Conflict of interest statement

L.D.L. reports grant and other financial relationship with Eisai, Ipsen, Merck Serono, MSD and BMS. T.I.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.031.

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